Uterine Sarcoma with Emphasis on Leiomycarcoma

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Disclosure Statement

"Please note... I DO NOT HAVE any affiliation/association with any laparoscopic power morcellator companies or companies that make/market alternative therapies for fibroids (uterine artery emboization, MR-guided focused ultrasound, Accessa device, DaVinci).

Definition and distinguishing characteristics

Sarcoma is an ancient (Greek) term for “fleshy excrescence”. Galen (130-200 c.e.) avoided the diseases. Numerous reports by anatomists and surgeons since then. Charles Bell (1772-1842) distinguished sarcoma from carcinoma, and Stout published a monograph in 1932 on the pathology and treatment of sarcoma.

Definition and distinguishing characteristics

Relatively small overall prevalence, widely disparate microscopic descriptions of non-carcinomatous, often lethal disorders (surgically excised or discovered at autopsy) obscured commonality. Published reports were mostly anecdotal until centers built libraries of pathologic material and created data bases.

Definition and distinguishing characteristics

James Ewing (1866-1943) first professor of Pathology at Cornell, Chief of Pathology at Memorial 1899 at the age of 33, classic monograph “Neoplastic Diseases” in 1919 with his original description of soft tissue sarcoma “sarcoma is a malignant tumor composed of cells of the connective tissue type”.

Definition and Distinguishing Characteristics

At the Memorial Hospital (MSKCC) pathologists developed a tradition of studying soft tissue sarcoma:

Stout, 1944, Liposarcoma.

Stout and Ackerman, 1947, LEIOMYSARCOMA OF SOFT TISSUES

Stewart and Treves, Lymphangiosarcoma

This impetus and attraction led to establishment of a data base from 1982 to the present including 8,000 completely annotated patients over the age of 16 years leading to the publication of “Management of Soft Tissue Sarcoma”, Brennan, M.F., Antonescu C.R.,and Maki, R.G., Springer 2013

Classification of Soft Tissue Sarcomas

- Fibrosarcoma
- Malignant Fibrous Histiocytoma
- Undifferentiated Spindle Cell
- Rhabdomyosarcoma (multiple types)
- Leiomyosarcoma
- Malignant peripheral Nerve Sheath Tumor
- Angiosarcoma
- Hemangiopericytoma

Classification of Soft Tissue Sarcomas

- And more than 7 others !!
- UTERINE SARCOMAS:
- Leiomyosarcoma 6.4/million/yr (LMS)
- Malignant Mixed Mullerian Tumor 8.2/million/yr (MMMT)
- Endometrial Stromal Sarcoma 1.8/Million/yr (ESS)

  Unclassified 0.7/million/yr

Tumor Biology

For all soft tissue sarcomas 3 dominant variables reflect tumor biology: histopathology, site, and tumor size. Analyses of gene profiles have now been accomplished for 20 types of sarcomas, with certain common gene patterns.

To date some of these pattern seem associated with tumor virulence, but these studies are performed after surgical interventions.

G.O.G. Classification of Uterine Sarcoma

- Mixed Homologous Mullerian Sarcoma
- Mixed Heterologous Mullerian Sarcoma
- Leiomyosarcoma
- Endometrial Stromal sarcoma
- “Other”

Staging ULMS and ESS

Staging uterine sarcoma (TNM and International Federation of Gynecology and Obstetrics [FIGO]

Primary tumor (T)*		
TNM Categories	**FIGO Stages**	**Definition**
Leiomyosarcoma and Endometrial Stromal Sarcoma		
TX		Primary Tumor cannot be assessed
TO		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in greatest dimension
T1b	IB	Tumor more than 5 cm

Staging uterine sarcoma (TNM and International Federation of Gynecology and Obstetrics [FIGO]

Primary Tumor (T) *		
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

Staging uterine sarcoma (TNM and International Federation of Gynecology and Obstetrics [FIGO]

Regional lymph nodes (N)		
TNM Categories	FIGO Stages	Definition
Leiomyosarcoma and endometrial stromal sarcoma		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Staging uterine sarcoma (TNM and International Federation of Gynecology and Obstetrics [FIGO]

Distant Metastasis (M)		
TNM Categories	**FIGO Stages**	**Definition**
Leiomyosarcoma and endometrial stromal sarcoma		
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

Risk Factors for Uterine Sarcoma

- African American 2-3 x > Caucasian
- Previous Tamoxifen Therapy 17/100,000
- Previous Pelvic Radiation
- Hx of Childhood Retinoblastoma
- Hx of Leiomyomatosis and Renal Cell Ca
- Uterine Myometrial Mass 1/500 (352-1000)

Presenting Symptoms

- Often absent , frequently diagnosed during or after surgery.
- ULMS occurs at 40-60 years of age, vaginal bleeding, pelvic and/or abdominal pain.
- Otherwise unexplained foul uterine discharge
- Less frequent: weight loss, weakness, lethergy, fever.

Diagnosis

Pathologic inspection of a specimen is required!

Non invasive diagnostic radiology is helpful but can not dependably distinguish Sarcoma from benign or cellular, atypical Leiomyoma (Fibroid)

Ultra-Sound: evaluates uterine cavity

MRI: defines depth of invasion or planes

CT or PET:evaluates extra uterine space

NONE OF THESE TECHNIQUES ASSURES DIAGNOSIS

RADIOGRAPHIC FINDINGS

- **SONOGRAPHY**: Uterine Mass, central necrosis, mixed echogenic areas, irregular vessel distribution via Doppler with low impedance to flow and high peak systolic velocity.
- **MRI**: incorporation of various techniques a positive predictive value of 50 to 100 % has been reported.
- All can be found in Fibroids and ULMS

HISTOLOGIC DIAGNOSIS

- **Essential Elements**: Hystologic type,Mitotic count, size, differentiation
- **Mitoses**: 0-5 / 10 High Power Fields=**Benign**
- 5-10 =**borderline,** or Smooth Muscle Tumor of Uncertain Malignant Potential **(STUMP)**
- More than 10 (per 10 HP fields)=**SARCOMA**

Additional Cellular Features

- Immuno-Histochemical Stains will show ER,PR desmin, smooth muscle actin, caldesmon.
- **Aneuploid Karyotype**, >50% have profound structural aberration such as deletion of chromosomes 1,13,14,16,18, and 22.
- Frequency of any specific aberration is <20%
- Leiomyomas have different patterns, but while there is some overlap, **ULMS is not from a "degenerated" Fiboid.**

Therapy

- Ideally, initial therapy should be **complete removal of all grossly identified tumor**, resulting in improved survival compared with patients having residual disease .
- Women who are peri or post menopausal should have bilateral salpingo-opherectomy with appropriate counseling, although there is no data to prove that survival is improved by this maneuver.

Therapy

- While metastasis to pelvic nodes in ULMS is rare without metastasis to other sites, most experts remove nodes if they are palpable or if there is abdominal disease (stage II and III) which is amenable to resection.

- If the disease is not resectable, extensive surgery will not improve survival, but may, in certain patients, **relieve symptoms** and **improve quality of life**.

Radiation Therapy

Pelvic Radiation, while it reduces local recurrence does not improve survival in patients who have had complete cytoreduction. If they recur, such patients will succumb because of distant metastasis, not local recurrence.

Chemotherapy

- There are useful chemotherapeutic regimens, but there is sparse robust evidence from large randomized studies clarifying the role of chemotherapy after complete cytoreduction in early disease.
- Currently there is an international collaborative comparing SARC 05 protocol to observation in patients with FIGO stage I completely resected. (GOG 277)

Chemotherapy

- MSKMC, 25 pts, completely resected ULMS

  Fixed dose rate Gemcytabine 900 mgm/m2 on days 1 and 8 , plus Docetaxel 75 mgm/m2
- Results: Stage I and II high grade 59% PFS 3 yrs
- At median follow up of 49 mos., 2 year PFS was 45 months and median PFS was 13 months for the whole group
- Hensley, et al. Gynecol Onc 2009

Chemotherapy

- SARC 005 Prospective, Multi-Institutional Phase II Trial disease limited to uterus, high grade ULMS, completely resected;
- Gemcytobine plus Docetaxel X 4, followed by 4 cycles of Doxorubicin
- Reporting on 47 patients: 89% received all 8 cycles, 3 yr PFS was 57% median time to recurrence 27 mos. Hensley et al. abstract 10021, J. Clin Onc 2010

Morcellation Query

- Do women with disseminated or advanced SARCOMA following morcellation have different prognoses and/or treatment considerations compared to those who present at the same stage and who did not have morcellation?

Morcellation Query

- There are no published prospective studies:
- Distinction between Leiomyoma and Leiomyosarcoma is impossible without tissue sampling. Prevalence is very low. If such a study were technically possible it would never be allowed.
- Several small retrospective studies suggest that re-operation after the diagnosis is made lead to upstaging, especially in sarcoma, that washings are negative even when there is advanced disease, and that in sarcomas survival is diminished. Since the second surgery is often delayed (40-60 days in some reports), the original stage is usually unknown.